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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/696,686	10/26/2000	Keith D. Allen	3866-4	4566
26619	7590	01/12/2006	EXAMINER	
JOHN E. BURKE GREENBERG TRAURIG LLP 1200 17TH STREET, SUITE 2400 DENVER, CO 80202			TON, THAIAN N	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/696,686

Applicant(s)

ALLEN, KEITH D.

Examiner

Thaian N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 12 August 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 80, 81 and 85-94 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 80, 81, 85-94 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 October 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 4/2/03.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

Applicants' Petition, under 37 CFR 1.137(b), filed August 12, 2005 to revive this application is granted. An action on the merits follows.

Applicants' Amendment and Response, filed 8/12/05, has been entered. Claims 1-79, 82-84, 95-104 are cancelled; claims 80, 81, 85-91 are amended; claims 80, 81, 85-94 are pending and under current examination.

#### ***Information Disclosure Statement***

Applicants' Information Disclosure Statement, filed April 2, 2003, has been considered.

#### ***Response to Arguments***

The prior rejection of claims 66 and 80, under 112, 1<sup>st</sup> ¶, for written description, is withdrawn in view of Applicants' amendment, deleting the phrase, "naturally occurring allelic variations" of T243.

#### ***Claim Rejections - 35 USC § 101/112***

The prior rejection of claims 66-69, 71, 73 and 74, under §101 and 112, 1<sup>st</sup> ¶, is rendered moot in view of Applicants' cancellation of the claims.

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80, 81, 85-94 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are directed to mice whose genome comprises a disruption in a TRP gene, said TRP gene encoding mRNA corresponding to the cDNA sequence of SEQ ID NO: 47, wherein the mouse exhibits a phenotype, relative to a wild-type mouse, reduced weight, decreased length, decreased ratio of weight to length, symptoms associated with cartilage disease, symptoms associated with cartilage disease, symptoms associated with kidney disease.

The instant specification teaches the screening of genomic libraries to generate pools of phagemid DNA, which were then screened for specific genes of interest, using long-range PCR (see Example 1, and Figure 1). The products of the PCR reactions were then separated by electrophoresis through agarose gel and then purified (Example 2). The specification teaches that the identification of flanking DNA for the target T243 gene (a trinucleotide repeat protein), and the analysis of the resultant homozygous knockout mice (Example 12). The specification teaches that a T243 targeting construct was generated, linearized, and electroporated into mouse ES cells, and upon confirmation of homologous recombination, blastocysts were implanted in pseudopregnant mice. The resultant chimeric offspring were then bred produce heterozygous T243 knockout mice, which were subsequently bred to produce homozygous offspring. It was found that the knockout T243 mice had decreased weight gain and lengthwise growth, when compared to wild-type or heterozygous littermates (p. 66 and Figures 9-10). Furthermore, post-mortem analysis revealed that these homozygous mice had abnormal cartilage and a generalized reduction of bone formation (p. 66) and dysplastic changes in both kidneys, where the kidneys were small and lacked normal architecture (p. 67).

The specification teaches that mouse models of trinucleotide repeat disorders hold great potential and promise for uncovering the molecular basis of these diseases, and developing therapeutic interventions (page 3, 1<sup>st</sup> full paragraph). The specification contemplates that the claimed knockout mouse can be used for methods of agents that affect a phenotype of a knockout mouse, to treat bone disease, cartilage disease, or kidney disease, by administering a putative agent (see pages 5-6). However, none of the asserted utilities of the knockout mice comprising a disruption in the T243 gene appear to be specific and substantial.

It is evident from the specification that T243 is identified by virtue that it is a encodes trinucleotide repeat protein. However, at the time of filing, the skilled artisan would not have found any of the contemplated utilities evident because the specification does not provide a correlation between a T243 deficiency, and any disease or condition. The specification is silent as to T243's role in any pathway or even what is observed in the normal expression of T243. While trinucleotide repeat proteins was known, the specification clearly shows that proteins harboring trinucleotide repeat tracts are unrelated and widely expressed (see page 2, 2<sup>nd</sup> full paragraph, first sentence) and that at least 12 different diseases are known to be caused by trinucleotide expansion mutations (see pages 2-3, bridging paragraph). Thus, neither the specification, nor the art at the time of filing, establish a specific function for the gene identified in the specification as T243, in any particular biochemical pathway, nor do they demonstrate a role for the deficiency of the T243 gene. Thus, in order to determine a specific utility for the mice, the skilled artisan would need to perform further research upon the claimed mice, in order to determine the correlation between the knockout of the T243 gene, and the observed phenotypes of reduced weight and length, and symptoms of cartilage, bone and kidney disease. If the function of the gene or its encoded protein are not known in the art, nor disclosed in the specification, at the time of filing, then the utility of the claimed invention is not apparent. Although disclosing phenotypic variations

between the T243 knockout mice, and control mice, the specification provides no evidence that the variations would be accepted as evidence of a particular biochemical pathway, a particular disease/condition, or as evidence of either a substantial or specific utility.

As set forth in the utility guidelines above, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient, absent a disclosure of what condition can be diagnosed. Similarly, a statement of therapeutic utility for an unspecified disease is non-specific, renders the purported utility of the claimed mice to be non-specific. The usefulness of the mutant mice, as models for disease, is not clear absent the assessment that they reflect a particular disease state. This leaves the skilled artisan to speculate the uses of the mice, cells, and methods, as claimed. Under the utility guidelines set forth above, requirement for further research or experimentation renders the claimed invention as lacking in a specific or substantial utility. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are not considered substantial utilities. The evidence of record has not provided any other utilities for the transgenic mice encompassed by the claims that are substantial and specific.

Since the mice have no determined specific function, the relation to any disease or condition is unknown, and further, because the phenotypes in the T243  $\pm$  mice are not specific to any one disease or condition, the artisan, at the time of filing, would not know how to use the mice or any data resulting from using the mice. To make such a determination, the skilled artisan would need to further research the mice, to determine if functions associated with the T243 gene are present in the mice, and then identify disease or conditions associated with the disclosed phenotypes. Since the mice and methods of using the mice lack specific or substantial utility, the methods of making the mice, the nucleic acid construct, and the cell claimed do not have utility. The utility of each of these is disclosed in the

specification to be based upon the utility of the mice. In light of the above, the skilled artisan would not find the asserted utility of the transgenic mice, targeting construct, and cells, encompassed by the claims to be specific and substantial.

### ***Enablement***

Claims 80, 81, 85-94 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 80, 81, 85-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

*Nature of the Invention/Breadth of the claims.* The claims are directed to mice whose genome comprises a disruption in a TRP gene, said TRP gene encoding mRNA corresponding to the cDNA sequence of SEQ ID NO: 47, wherein the mouse exhibits a phenotype, relative to a wild-type mouse, reduced weight, decreased length, decreased ratio of weight to length, symptoms associated with cartilage disease, symptoms associated with cartilage disease, symptoms associated with kidney disease.

*Guidance of the Specification/The Existence of Working Examples.* The instant specification teaches the screening of genomic libraries to generate pools of phagemid DNA, which were then screened for specific genes of interest, using long-range PCR (see Example 1, and Figure 1). The products of the PCR reactions were then separated by electrophoresis through agarose gel and then purified (Example 2). The specification teaches that the identification of flanking DNA for the target T243 gene (a trinucleotide repeat protein), and the analysis of the resultant homozygous knockout mice (Example 12). The specification teaches that a T243 targeting construct was generated, linearized, and electroporated into mouse ES cells, and upon confirmation of homologous recombination, blastocysts were implanted in pseudopregnant mice. The resultant chimeric offspring were then bred produce heterozygous T243 knockout mice, which were subsequently bred to produce homozygous offspring. It was found that the knockout T243 mice had decreased weight gain and lengthwise growth, when compared to wild-type or heterozygous littermates (p. 66 and Figures 9-10). Furthermore, post-mortem analysis revealed that these homozygous mice had abnormal cartilage and a generalized reduction of bone formation (p. 66) and dysplastic changes in both kidneys, where the kidneys were small and lacked normal architecture (p. 67).

*State of the Art/Predictability of the Art.* The state of the art of producing knockout transgenic animals, particularly with regard to the unpredictable phenotype, has been addressed in the prior Office actions (see p. 11, of the Office action, mailed 2/24/03, and p. 12 of the Office action, mailed 7/5/02). This is germane to the instant rejection, because the broad claims do not recite a particular phenotype for the claimed mice. Thus, one of skill would not find an enabled use for these mice. For example, if the mice exhibited wild-type phenotypes, they would not be discernable from a wild-type mouse, and could not be used in any contemplated use by the specification (for example, in screening using agents to treat kidney disease). The unpredictability in the art of producing knockout mice is

further supported by Leonard [**Immunological Reviews**, (148): 98-113 (1995)] disclose mice with a disruption in the  $g_c$  gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (Abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths [**Microscopy Research and Technique**, 41:344-358 (1998)] taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). Thus, at the time of filing, the resulting phenotype of a knockout was considered unpredictable. Thus, absent a specific phenotype, the claimed knockout mice have no enabled use.

*The Amount of Experimentation Necessary.* The broad claims fails to provide an appropriate phenotype for the claimed mice. Absent an appropriate phenotype, one of skill in the art would not know how to use these mice. The breadth of the claims encompass both heterozygous and homozygous mice, however, the specification is not found to be enabling for this breadth; the specification clearly teaches that the reduction in growth and weight gain, the bone, cartilage and kidney mutations were only observed in homozygous mice (see pages 66-67).

Accordingly, in view of the lack of appropriate phenotypes recited in the claims for the T243 knockout mice, the teachings in the specification, which clearly show that only homozygous mice exhibit the claimed phenotypes that provide for their enabled use, the unpredictable state of the art, with regard to the resultant phenotype in knockout mice, the lack of enabled use for mice lacking an appropriate phenotype, and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

### ***Written Description***

The prior rejection of claims 66-69, 71, 73 and 74, under §101 and 112, 1<sup>st</sup> ¶, is rendered moot in view of Applicants' cancellation of the claims.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 80, 81, 85-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 80 contains the phrase "corresponding to the cDNA sequence of SEQ ID NO: 47." However, the term "corresponding to" does not necessarily mean that those exact bases are replaced. The definition of corresponding to found at <http://www.thefreedictionary.com/corresponding> (The Free Dictionary by Farlex [online], term "corresponding" [retrieved on 1/6/06]. Retrieved from the Internet, URL: <http://www.thefreedictionary.com/corresponding?p>>.) has definitions that indicate the term can mean related to, connected to, associated to, and similar in position or purpose. Given the multiple definitions in the art, and the lack of a definition of "corresponding to" in the specification, the metes and bounds of the claim is not clear. As any replacement is related to, connected to, associated to and similar in position or function, the claim is being interpreted to include any bases replaced. Claims 81 and 85-94 depend from claim 80.

**Adj. 1. corresponding** - accompanying; "all rights carry with them corresponding responsibilities"

related, related to - being connected or associated; "painting and the related arts"; "school-related activities"; "related to micelle formation is the...ability of detergent actives to congregate at oil-water interfaces"

**2. corresponding** - similar especially in position or purpose; "a number of corresponding diagonal points"

similar - marked by correspondence or resemblance; "similar food at similar prices"; "problems similar to mine"; "they wore similar coats"

3. **corresponding** - conforming in every respect; "boxes with corresponding dimensions"; "the like period of the preceding year"

comparable, like

same - closely similar or comparable in kind or quality or quantity or degree; "curtains the same color as the walls"; "two girls of the same age"; "mother and son have the same blue eyes"; "animals of the same species"; "the same rules as before"; "two boxes having the same dimensions"; "the same day next year"

4. **corresponding** - agreeing in amount, magnitude, or degree; "the figures are large but the corresponding totals next year will be larger"

in proportion to, proportionate

commensurate - corresponding in size or degree or extent; "pay should be commensurate with the time worked"

### ***Claim Rejections - 35 USC § 102***

The prior rejection of claims 70, 72, 75, 77-79, 81 and 84 under 35 U.S.C. 102(b) as being anticipated by Hodgson *et al.* is withdrawn in view of Applicants' amendment to the claims, which now recite that the TRP gene encodes an mRNA that corresponds to the cDNA sequence of SEQ ID NO: 47.

The prior rejection of claims 70, 72, 75, 77-79 under 35 U.S.C. 102(b) as being anticipated by Lia *et al.* is withdrawn in view of Applicants' amendment to the claims, which now recite that the TRP gene encodes an mRNA that corresponds to the cDNA sequence of SEQ ID NO: 47.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 80 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (cited on the Information Disclosure Statement, filed 4/2/03) when taken with Carninci *et al.* (**Methods Enzymology**, 303: 19-44 (May 1999), and attached alignment of SEQ ID NO: 47 (GenCore alignment of SEQ ID NO: 47 to Carninci *et al.*, cited above).

The claims are directed to a mouse whose genome comprises a disruption in a TRP gene, wherein the TRP gene encodes mRNA corresponding to the cDNA sequence of SEQ ID NO: 47 (claim 80), wherein the mouse is homozygous for this disruption (claim 81). Note that the term "corresponding to" is not necessarily specific to the cDNA sequence of SEQ ID NO: 47, but anything that corresponds to this sequence. Please see the rejection above under 35 U.S.C. § 112, second paragraph. Thus, any replacement chosen is viewed as "corresponding to" the cDNA sequence of SEQ ID NO: 47.

Capecchi teaches knockout technology applied to mice, and specifically with respect to the disruption of the *HoxA-3* gene and as the method of producing the same applies to determining the *in vivo* biological function of any known gene of interest. For example, Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning of the gene to the manifestation of disease (See page 41, column 2, 2nd full paragraph). Capecchi further discloses the essential components of a targeting vector (page 38, column 3; and page 39, columns 1 & 2), and the steps involved for targeted gene replacement in ES cells as well as in mice (pages 36-39 and diagrams) to produce both heterozygous and homozygous knockout mice. Capecchi teach the isolation of tissue from transgenic mice for analysis. See p. 41, 1<sup>st</sup> column. Capecchi differs from the claimed invention in that the targeting construct does not contain flanking nucleotide sequences that homologously recombine with the

genomic T243 gene (SEQ ID NO: 47). However, prior to the time of the claimed invention, Carninci *et al.* teach a sequence with 97.8% identity to sequence of SEQ ID NO: 47 (see attached alignment). Although this sequence does not teach the genomic sequence of the T243 gene, it would have been well within the skill of the ordinary artisan to use this cDNA sequence screen a mouse genomic library to obtain a genomic fragment, which could then be used to produce a targeting vector, such as that instantly claimed. Note that absent any phenotypic requirement the claimed invention is rendered obvious in light of the combined teachings of Capecchi and Carninci *et al.*

Accordingly, in view of the combined teachings of Capecchi and Carninci *et al.*, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to modify the knockout technology of Capecchi, by use of a targeting vector for disruption of the T243 gene in a mouse ES cell with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as it was an art-recognized goal to determine the physiological role of gene of interest by the generation of a knockout mouse.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via

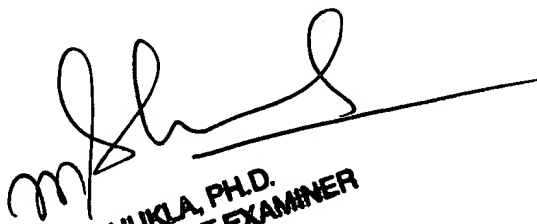
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the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*tnt*

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